ANIMAL HEALTH INSTITUTE

Representing manufacturers of animal health products

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Division of Dockets Management
U.S. Food and Drug Administration
HFA-305
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2004N-0479 – Draft Risk Assessment of Streptogramin Resistance in Enterococcus faecium Attributable to the Use of Streptogramins in Animals

The ANIMAL HEALTH INSTITUTE ("AHI") submits these comments to the Docket number 2004N-0479 dated November 23, 2004 requesting input on the Agency's draft risk assessment of streptogramin resistance in Enterococcus faecium attributable to the use of streptogramins in animals.

AHI is the national trade association representing manufacturers of animal health products – the pharmaceuticals, vaccines and feed additives used in modern food production, and the medicines that keep livestock and pets healthy.

General Comments on the Process, Format, Scope and Content

CVM is to be commended for undertaking a quantitative risk assessment on a most complex issue. The quantitative risk assessment approach avoids over-reliance on a qualitative risk assessment, which seems to be what was done by APVMA in Australia for their review of virginiamycin (APVMA, 2004); or the European political decision approach following the invocation of the precautionary principle to remove the growth promotion claims of virginiamycin.

However, there is no reason the process should have taken 4 years to reach draft stage. Other risk assessment approaches (Hurd, 2004; Cox and Popken, 2004, Kelly et al., 2004) etc. have been completed and published in far less time). The information found within the risk assessment is now dated; a perusal of the reference list suggests that most of the papers used to write the document were published in 2002 or before. The authors should take this opportunity to add the most recent information on streptogramin-resistant *E. faecium*. For example, there is new information available on the efficacy and usage of QD to treat VREF, the likelihood that QD will be used to treat VREF, the concurrence of streptogramin resistance markers in animals and humans and the potential acquisition of

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QD resistance during therapy. Arguably, this document is about the modeling but readers will find this document most credible if it is up-to-date.

Recent work has begun to show that a risk:risk, risk-benefit or risk:trade-off approach should be undertaken (Cox and Popken, 2004). Human health benefits that accrue due to the use of a given antibiotic should be evaluated as well as the risks; and a determination of the ratio of risk to benefit made. In support of this point, at the October, 2004 VMAC meeting to review a new macrolide, tulathromycin, for use in cattle per Guidance 152, VMAC stated that "animal welfare" should be a criterion for evaluation. Provided that this precedent is applicable to the situation with other antibiotics, such as streptogramins, it seems as though this aspect of the current risk assessment must be addressed. AHI encourages CVM to incorporate this aspect into the next iteration.

Other risk assessments have used multidisciplinary panels; however, the listing of CVM authors excludes expertise particularly in human infectious disease practices, epidemiology, food microbiology, etc., so the next iteration would benefit from input from a multi-disciplinary panel. Many of the deficiencies noted in the document could have been addressed by persons with the appropriate expertise.

The stated objective of the risk assessment was to determine the risk of VREF infected humans failing Synercid therapy. But, the risk estimates are based only on the potential for streptogramin resistant *Enterococcus faecium* infections (that are also vancomycin resistant) to be exposed to Synercid, not whether that exposure will actually result in a less than anticipated favorable response to treatment. The draft report makes the implicit assumption that clinical treatment outcome is strongly correlated with the MIC. This may or may not be relevant for patients likely to be treated with Synercid for an *E. faecium* blood stream infection owing to confounding factors of the patient population (e.g. immune status, other health issues such as kidney function, etc.). Based on the fact that only low level resistance (MIC $\leq$4 ug/ml) is found in human isolates, there may be little clinical impact. It appears that somewhere in the process, the focus shifted and became confused with the relationship between MICs, clinical outcome and risk. The draft report would be improved by working toward a consistent objective.

The various sections of the risk assessment lack congruence and the overall cohesiveness of the document could be improved by some judicious editing. For example, the release and exposure sections of the document suggest that gene transfer from animal-derived enterococci to human enterococci is the primary route by which people will acquire streptogramin-resistant *E. faecium* infections. However, the calculations in the consequence section rely on the assumption that colonization by animal-derived streptogramin-resistant *E. faecium*, as represented by the use of genogrouping data, is the primary means by which humans will acquire such an infection. The document does state that the authors believe that people are more likely to acquire *E. faecium* infections that are not treatable with either streptogramin or vancomycin by co-infection with SREF and VREF than by gene transfer. However, given the amount of information presented on gene transfer, this comment has the appearance of an

afterthought. The release and exposure sections would provide a more effective introduction to the consequence section if the material on gene transfer was condensed and the material on co-infection was expanded. The idea of gene transfer has long been speculated as the mechanism by which risk to human health from antibiotic-resistant enterococci will occur. Co-infection represents a departure from this broadly accepted idea and as such, requires more explanation. The authors should consider including scientific data on this topic - what is the precedence for co-infection?

The scope of the risk assessment should include consideration of the epidemiology of spread of SREF within a healthcare facility and needs further analysis. It remains to be explained how the introduction of one patient, with transient SREF in their intestinal tract, can be a "shedder" into a healthcare facility; and that strain becomes established and maintained in the facility as a nosocomial strain. This should be contrasted with nosocomial enterococcal infections in patients that become streptogramin resistant during the course of treatment with Synercid; and how those strains become epidemic within a facility. A recent discussion of the type of epidemiology that is involved is provided (Smith et al., 2004).

Application to Guidance 152

The quantitative approach shows the value of extensive research on clinical outcome data as opposed to simply using a "look up" table in Appendix A in Guidance 152 where streptogramins are categorized as "highly important". There is no way this assessment could have been conducted using the qualitative ranking of "highly important". Since this draft shows that there may be clinical data available to actually determine the sequence of hospital treatment protocols and outcomes for Synercid, CVM is encouraged to ask FDA CDER to revise Appendix A by considering actual clinical information or allowing drug sponsors to provide that data in lieu of simply using the "look up" table.

On page 67, section 4.7, it is stated that "*conclusions based in part on qualitative exposure assessment are likely to be overly conservative*" We agree. It is further stated that after the presentation of the animal for slaughter, the transport of resistant bacteria through the food chain, and the factors contributing to human exposure are primarily human controlled factors. In essence, that is why food hygiene during processing, in the home and in food service has the greatest impact on controlling transfer of resistant or susceptible microorganisms. This has been our major criticism with GFI #152 that uses simple per capita consumption and rough approximations of pathogen prevalence on raw products to determine level of exposure. Recent CDC FoodNet data has shown that improvements in food hygiene, attributable to the full implementation of post-harvest HACCP interventions, has reduced the incidence of bacterial food borne disease (MMWR, 2004). Given the reality of reduced carcass contamination, and thus meat contamination, the draft report scenario that assumes 100% of the streptogramin resistant enterococci could come from animal sources cannot be valid. The exposure assessment does not factor in further processing or cooking of the contaminated meat which would

reduce the exposure to SREF to near zero. A zero exposure scenario is more likely a 100% exposure. If the 100% exposure scenario was likely, then human isolates would routinely be found with high level resistance. In reality, MIC frequencies are different for enterococci isolated from animals and humans; resistance (MIC $\geq$ 32μg/mL) rates in animal derived isolates are relatively high while human isolates show a low (0-4%) prevalence of high MICs.

Although the draft risk assessment purports to make no risk management recommendations, it is clear that intervention steps would be most effective closer to the patient, rather than on-farm. Food hygiene, hospital infection control, appropriate antibiotic use in patients, etc., appear to be key areas. There is no indication that any changes to the label indications of the virginiamycin product line would have any effect on the human use of Synercid. Although the authors clearly point out that risk management strategies were not a part of the current draft risk assessment, there is no doubt that this work will be used by some organizations for that very purpose.

Specific Technical Comments

Page 69 indicates that in order to conduct this assessment at all a **"causal process was assumed to exist between exposure to hazardous agents and increased risks of adverse health effects..."** Given that the causal process was ***assumed*** to exist, but was not shown by listing the temporal association data on page 3, nor convincingly presented throughout the remainder of the document, it must be questioned as to whether there was even enough evidence upon which to conclude that virginiamycin use in animals presents a hazard, let alone a risk. The following points reinforce this conclusion:

- The exposure assessment does not factor in processing or cooking of the contaminated meat which would reduce the exposure to SREF to near zero. A zero exposure scenario is more likely than a 100% exposure.

- A large proportion of SREF did not possess genes known to encode for resistance nor was the majority of human isolates similar in MIC findings to animals. Page 71 states " **Unequivocal molecular genetic evidence for animal bacteria origins of streptogramin resistance among human-adapted *E. faecium* has yet to emerge"**

- The scenario that assumes 100% of the resistance could come from animal sources cannot be valid. If this were the case human isolates would routinely be found with high level resistance. MIC patterns are different from animals and humans; resistance rates in animal derived isolates are relatively high while human isolates show a low (0-4%) prevalence. Indeed, MIC's for animal isolates were routinely in the 16-32 ug/ml range while vast majority of human isolates were in the 4 ug/ml range. The authors state that this is **"inconsistent with the postulated attribution of human streptogramin resistance from animal sources"**

- The risk assessment does not really estimate streptogramin treatment failures, a fact that should be more clearly emphasized in both the executive summary and the body of the document. The document does state that a SREF infection is not equivalent to a treatment failure. This position could be reinforced by the discussion of two important points. First, vancomycin and Synercid® do not represent an either/or treatment situation: patients are not treated with one or the other. Other antibiotics are available and in fact, linezolid is more likely to be used to treat VREF infections than Synercid®. Second, susceptibility testing would be used to determine the best course of therapy for a hospitalized patient infected with *E. faecium* and if strains resistant to vancomycin and streptogramins were implicated, the patient would be given alternate therapy and would have no chance to experience streptogramin treatment failure. This is the clinical portion of the assessment where the expertise of an infectious disease physician would have been useful.

Specific comments

(Note: where line references are used headings and sub-headings are not counted. P = page, L = line, par = paragraph, B = bullet)

Ref	**Comment**
Piii Executive Summary	The risk assessment does not support a food attribution factor of 100% and, as written, the discussion of this scenario in the executive summary could be misleading to the casual reader. The intent of the authors may have been to lend validity to their model: as the attribution changes 10-fold so too does the number of expected cases of streptogramin-resistant *E. faecium* infection. If so, this information should be confined to the consequence section of the risk assessment in order to prevent any misunderstanding. The authors might also consider including information on how the number of cases changes if the attribution is changed 10-fold in the other direction, i.e. 1%. If there is a compelling reason to leave the 100% food attribution passage in the executive summary, then it should be clearly stated that this scenario speaks to the sensitivity of the method and is not one that is supported by the scientific data.
P3 L16	Replace "the existence" with "the potential existence" as the existence of the pathway has not been clearly demonstrated.
P3 B3	Comments should be restricted to *E. faecium* data only.

P3 B4	Comments should be restricted to transfer of genetic determinants conferring resistance to streptogramin antibiotics only. In addition, The reference to transfer of genetic determinants that "*has been demonstrated to occur readily among enterococci in controlled studies*" should make it clear that these controlled studies were either conducted *in vitro*, or in germ-free animals, and not in the human intestine as is implied by the present wording.
P8 L11 P9 L22	"Clearly if new data or information…incorporating the new data into the assessment." We recommend the authors incorporate the effect of contemporary linezolid prescribing practice for the treatment of VREf. The current draft assumes Q/D use as a first line treatment for VREf. This assumption is no longer true so the models should be amended accordingly.
P10 L26	"Note that the acquisition of resistance not likely to occur through single or multiple mutations, but through horizontal gene transfer." The apparent differences in the genetic basis of resistance between animal and human origin strains identified elsewhere in the draft report suggest that if this horizontal transfer pathway is important it is only the human use of streptogramins that will determine the future prevalence of streptogramin resistance in human *E. faecium*.
P14 par 1	The implications of this paragraph are unclear. It may be that the authors are highlighting the relatively high incumbent level of nosocomial antimicrobial resistance observed in aged care patients. This is interesting but would appear to be not pertinent to the examination of animal derived SREf.
P15 L14	"…and may transfer resistance determinants to human communal Enterococcus bacteria." The transfer of resistance determinants to human communal Enterococci is speculative. This passage should be deleted as it does no more than reiterate the speculative hypothesis that forms the basis for undertaking this review.
P23 L7	Clarification of the level of clinical efficacy afforded by Synercid® is fundamental to this risk assessment. Clearly should Synercid® be shown to be less than 100% effective, any assessment of potential loss of the clinical value of Synercid® must be downgraded to reflect this lack of efficacy. The authors should follow up on the statement "Clinical studies…are presently under way" as the document was dated September 21, 1999 and the studies mentioned should be complete.

P25 L21	Whereas *E. faecalis* accounts for 80 to 90% of clinical isolates while *E. faecium* accounts for less than 10%, linezolid, which is effective against both, would be expected to be the treatment of choice after vancomycin if susceptibility testing is not conducted prior to initiation of treatment (note that Synercid® is effective only against *E. faecium*).
P26 L5	"Recent data…". Provide reference.
P26 L12	"The hardiness of enterococci…some types of food processing." What types of food processing? Provide reference.
P29 L16	"The presence of a resistance mechanism…within the clinically manageable range." If the disease is clinically manageable, then any such case cannot be considered a treatment failure. Was this taken into consideration when calculating potential Synercid® failure, as many of the human isolates referred to in the RA appear to be only "partially" resistant (i.e. a lower resistance breakpoint than animal isolates).
P30 L24	Impact of clonally mixed infections. Under a clonally mixed infection containing SREf and VREf, the treatment regimen would presumably be linezolid. However, if the populations were also both concurrently linezolid resistant the initial treatment regimen of vancomycin would be followed by Q/D. The impact would be limited to a prolongation of therapy. If the clonal mix was identified as such at the outset concurrent therapy would be expected to control the infection in a time similar to the normal mono-therapy. As for the entire risk assessment the preceding comment assumes that antibiotic sensitivity has a high correlation with treatment efficacy. This may not be the case with the class of patient with an *E. faecium* BSI.
P31 L2	Same comment as for P30 L24

P34-37 Table 3-1	While the authors use the NCCLS breakpoint of 4μg/mL, they correctly acknowledge elsewhere in the report that clinical efficacy may still be retained at levels above 4μg/mL. In this regard the inclusion of isolates with lower MICs in the range of 4 – 8 μg/mL in the resistance column is misleading. [see P53, L23 Butaye (2003)] Has misidentification of *E. faecium* and *E. faecalis* been corrected for in these tables? If not, an additional column with this correction would be informative and provide an improved resource for subsequent reviews of this work in the light of new data. The author reports elsewhere (p55) that misidentification of *E. faecalis* as *E. faecium* may be as high as 20% and misidentification of *E. faecium* may be as high as 94.7% in total.
P34-37 Table 3-1	The Aarestrup et al., 2000b data for broilers and pigs demonstrate a difference in resistance rates of the same isolates to Synercid® (Q/D) and Virginiamycin, with much lower rates attributed to Q/D. Does this indicate that cross-resistance between virginiamycin and Q/D is less than 100%?
P38-39 Figure 7 & 8	The figures appear to include only one human data point each. Does this imply that streptogramin resistance in humans has risen from zero subsequent to the cessation of animal use? If not, what point is the author alluding to with the inclusion of a single data point? If this is the only year for which DANMAP reports human data, it should be so stated.
P38 Figure 7	We note that the DANMAP broilers and broiler meat figures suggest that live animals maintain a level of resistance of approximately 30%, while the meat resistance levels have dropped to near zero. This would appear to indicate that something other than the ban of virginiamycin, such as better hygiene during processing, has decreased meat contamination.
P40 L15	Please clarify what "poultry data from European countries (those that permit use of virginiamycin)" are being referred to here, as poultry data in Tables 3-1 and 4-1 all appear to be from countries that do not allow use of virginiamycin.
P41 Ls 9-11	See comment for P30 L24 and P34 – 37 Table 3-1.
P42 Exposure Assessment	The exposure assessment does not factor in processing or cooking of the contaminated meat, which would reduce the exposure to SREf to near zero. A zero exposure scenario is just as likely as a 100% exposure.

P44 Butaye ref	It is not clear how this uncertainty concerning the apparent less than complete cross-resistance between virginiamycin and quinupristin-dalfopristin (noted both here and in the second comment for P34-37, Table 3-1) has been incorporated into the overall risk assessment in this draft report. Presumably less than complete cross-resistance would tend to lower the overall risk estimate.
P45-46 Table 4-1	Consistent with the draft report authors' comments on this issue, the use of 4μg/mL as a breakpoint will tend to over-report resistance levels relative to the expected clinical endpoint. The relatively low MICs found in human isolates relative to animal isolates does not tend to support the hypothesis that streptogramin resistance in human *E. faecium* originates in animal *E. faecium*. Has misidentification of *E. faecium* and *E. faecalis* been corrected for in these tables? If not, an additional column with this correction would be informative and provide an improved resource for subsequent reviews of this work in the light of new data. The authors report elsewhere (p55) that misidentification of *E. faecalis* as *E. faecium* may be as high as 20% and misidentification of *E. faecium* may be as high as 94.7% in total. There is an assertion made in the text that resistance observed prior to 1999 is likely to be related to animal transfer. Given the phenotypic differences observed between resistance observed in human and animal *E. faecium* it may be more likely that resistance observed prior to 1999 reflects misidentification of *E. faecium*.
P53 L2-4	The higher levels of community SREf are likely to be spurious reflecting the misidentification of *E. faecium*.
P53 L8	Eliopoulis' work tends to refute the hypothesis that de-novo nosocomial resistance is unlikely and that resistance in humans is the result of horizontal transfer. These data would suggest that the upper bound of resistance in humans attributable to animal use of virginiamycin is not 100%, as suggested in this RA.
P53 L17	Del Campo observed that MICs in *E. faecium* from food handlers were lower than those of the general population. This observation tends to refute the hypothesis of zoonotic origin.
P55 L28	Acquired resistance tends to be overestimated due to misidentification of *E. faecium*. Presumably, correcting for the likely overestimates of resistance would tend to lower the overall risk estimate.

P56 last L–P57 L3	"Sorensen…in concentrations similar to that present in meat…" It would appear that the subjects were fed levels found in raw pork, while pork is usually cooked before consumption. Since it is not known if lower levels of contamination (i.e. those found after cooking) would give the same results, these data are meaningless to the current RA.
P57 L21	"…continued consumption of contaminated meat and poultry products…" In order for this to occur, there would have to be continual cross-contamination from meat to other foods or back to the meat in question (i.e. continuous mishandling of food) as proper cooking will eliminate the contamination.
P59 L7	It is unclear how the authors have reached this conclusion regarding horizontal transfer. Further elucidation of this point would be valuable. Given the apparent differences in resistance determinants from animal and human sources further investigation into human to human horizontal transfer may be useful.
P59 par 2	This work appears to be greatly removed from the real world *in-vivo* scenarios under investigation, accordingly the work appears to be of limited relevance to the central issue. If the assertion of low relevance is valid this paragraph should be deleted.
P59 par 3	Transfer of resistance determinants other than streptogramin resistance determinants are of low relevance to this review. If the assertion of low relevance is valid this paragraph should be deleted.
P59 par 4	An alternate interpretation of this clonal identity is transient carriage of zoonotic strains, or multiple transient carriage. This would seem more likely than the otherwise unsupported hypothesis of zoonotic resistance determinant transfer.
P60 par 2	Alternative interpretations are that resistance observed prior to 1999 reflects misidentification of *E. faecium*; or may reflect pristinimycin use in humans (or human-to-human resistance transfer between pristinimycin treated and non-treated patients).
P61 L2	"These results are not consistent with…" Same comment as for P53 L28.

P63 Table 4-4	Jensen et al and Haroche et al data from the Netherlands demonstrate differences in prevalence of resistance genes from animals (poultry and pigs) and the human community in that animals have a lower % of *vat*(D) compared to *vat*(E), while humans have a reversed ratio. These data would suggest that resistance is not transferred from animal to man, and demonstrate that 100% attribution of human resistance to virginiamycin use in animals is not likely.
P63 Table 4-4	Werner at al data from Germany demonstrate differences in prevalence of resistance genes from animals (poultry, broiler carcasses and pork) and hospitalized patients in that animals have a lower % of *vat*(D) compared to *vat*(E), while humans have a reversed ratio. These data would suggest that resistance is not transferred from animal to man, and demonstrate that 100% attribution of human resistance to virginiamycin use in animals is not likely.
P67 par 3	Conclusions. That "...resistance determinants on retail meats may contribute to direct human exposure." is presumably the basis for initiating this report, however, as the authors have noted human colonization with zoonotic strains of *E. faecium* has not been shown to result in anything beyond transient carriage. The draft report cites that *E. faecium* streptogramin resistance determinant transfer data from *in-vitro* models has only been replicated in highly contrived *in-vivo* models using gnotobiotic mice. The report does not provide support that *in-vivo* transfer of animal derived resistance determinants is likely in the food-human host interface. In this citation of the background incidence of streptogramin resistance in *E. faecium* cited at 0 to 4% the report should reiterate that the higher level (4%) is most likely associated with misidentification of *E. faecium* and therefore the true incidence is likely to be much closer to 0% than 4%.
P68	The disclaimer regarding "difficult to assess" is unnecessary since CVM conducted a laborious assessment using all available data. It was concluded that the evidence is very sparse to support the theory of direct flow of resistant determinants to man and if it occurs at all it is extremely limited. This lack of evidence coupled with the special conditions that must be present for SREF to even impact human health, would suggest that it is relatively easy to conclude that virginiamycin use in animals has little or no impact on streptogramin effectiveness in humans.

P71 L6	The authors appropriately state that the consequence pathway has been established using avoparcin-vancomycin surrogate data. While this may be acceptable to further explore the consequence hypothesis, this approach does not provide a robust foundation on which to base further interpretation or decision making. Accordingly the authors (CVM) should remain vigilant that future users of this work only do so in an appropriate manner. If this is impractical, we suggest this component of the report should be omitted.
P73 Table 5-2	Food handling, food processing, food preparation (such as cooking) are all factors that affect consequences of microbial pathogen exposure. These factors should be included in the table under "environmental".
P76, par 1	"This risk assessment seeks an estimate of the number of cases **of Synercid® failure due to** streptogramin-resistant..." as this was the objective of the RA.
P76, par 2	Because linelozid (L) has become the drug of choice for VREf infections, the upper limit on the number of cases that are "at risk" of streptogramin therapy should be based on VREf/LREf.
P78, Table 6-1	This table requires clarification. For example, is the NNIS *Average Daily Cases* Median (239) outside of the Interquartile range (150-218), and if so, how was this calculated?
P82, s6.3.3	The role of linezolid should be reflected in this series of equations such that the terminal formula would reflect the triple resistance status of S+L+VREf as rational clinical therapy would ensure quinupristin-dalfopristin was only used should the infective organism be resistant to both linezolid and vancomycin.
P83, L17	The assumption that all streptogramin resistance in the non-hospitalized community is due to food animal uses of virginiamycin could be acceptable as an upper-bounding assumption (even though data referred to in this report demonstrate that this is not likely), however, the values ascribed (0-4%) appear not to be corrected for misidentification of *E. faecium*. Correction for the likely level of misidentification should be incorporated prior to further use of this incidence estimate.
P85, table 6-2	The role of linezolid in the treatment of VREf should be incorporated into this model.

P88, par 3 and footnote 9	Footnote 9 suggests that data were available through 2003, yet the authors only mentioned 2001. New data from IMS for the first 3 quarters of 2004 suggest that linelozid sales have climbed dramatically from 2001 – 2004, while Synercid® sales have dropped considerably during the same time period (>40%). Such a change would have a large impact on the Model 2 results. The authors should consider updating the risk assessment with 2004 data.
P88, eq 10	The "x" sign should be a division sign.
P89, L8	Exact usage data by indication may not be available, however, given that this draft report frequently uses surrogate data it would be reasonable to estimate the proportion of Synercid® used for non-VREf indications from isolation frequency data for VREf, MRSA, and resistant *Strep pygenes*. The estimated 119,000 Synercid® treatment days for VREf should be reduced proportionally.
P89, par 2	Moellering et al (1999. J. Antimicrobial Chemotherapy, 44, 251-261) have shown a mean duration of treatment of VREf patients with Synercid® of 14.5 ± 10.7 days. Ament et al (2002. American Family Physician, 65, 663-670) state in Table 4 (P 667) that linelozid recommended duration of treatment for VREf is 14 – 28 days. These data would suggest that use of 7 days of Synercid® therapy per VREf case is overly conservative. Because the number of treatment days has a direct impact on the calculated number of infections, using this overly conservative number has resulted in overestimates of the virginiamycin/Synercid® impact with Model 2.
P90, table 6-3	Mean estimate numbers should be reduced as noted in previous comments.
P92, L13	The role of linezolid in the treatment of VREf should be incorporated into this model.
P93, Table 6-5	The content of this table should be amended to reflect the issues raised in previous points. For example, Model 2 results, which are far higher than results from either of the other models, would be lower if 2004 IMS data were used, and if the overly conservative "7-day treatment" was increased to a more realistic value (10 – 14 days).

P94, par 2	What was the basis for the CVM's interest in 100% attribution ? Given that this draft report has shown a lack of support for the food attribution hypothesis the CVM should remain vigilant that future users of this work only do so in an appropriate manner and that the 100% attribution calculations are highlighted as un-based, hypothetical upper bounding numbers and are not reflective of a real scenario.
P95, par 3	"The least sensitive variable… … is the probability that the infection is *Enterococcus spp.*" This statement is intuitively improbable, while this may be mathematically correct, does this comment undermine the veracity of the model ?
P99, L4	The report previously highlighted additional work commissioned by CVM on the genetic basis of resistance. Surely this could have a material impact on risk estimates as currently the risk estimates are based on illustrative food attribution rates only.
P99, bullets 7, 8 & 9	Bullet 7 is innately inconsistent with bullets 8 & 9 regarding food attribution.
P99, bullets 8, 9, 10 & 11.	Clarity of meaning for bullets 8 through 11 would be enhanced by adding the word "although illustrative only" prior to the food attribution assumption phrases.
P 114	"NCCLS" is missing from Appendix II.

Conclusions

The report identifies many weaknesses in the chain of assumptions linking the use of virginiamycin in animals with Synercid® resistance in humans. However the report fails to give sufficient emphasis to these weaknesses, so that the final risk estimates overemphasize the possible animal attribution for human infections.

Aside from the shortcomings in this initial, outdated draft, the draft risk assessment proves this process is an extremely enlightening means of determining if a potential problem exists. In this case using a risk assessment process to map the potential control points for resistance selection, exposure, and impact, and utilizing available data, it is evident that there are significant hurdles throughout the food production and processing chain which significantly reduces the potential of animal derived resistant bacteria to impact human health.

With the present information and modeling efforts, it is highly questionable that further effort is actually needed to refine the risk assessment. For the reasons outlined in the previous section, CVM is encouraged to conclude that this effort represents an extensive hazard identification exercise and there was not sufficient evidence upon which

to conclude that virginiamycin use in animals presents a hazard, let alone a risk, to public health.

AHI thanks CVM for the opportunity to comment.

Sincerely yours,

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References:

APVMA http://www.apvma.gov.au/chemrev/virginiamycin.shtml

Cox, Jr., L.A. and D. A. Popken. 2004. Quantifying Human Health Risks from Virginiamycin Used in Chickens.Risk Analysis 24:271-28

Cox, Jr., L.A. 2004, Potential human health benefits of antibiotics used in food animals: a case study of virginiamycin, Environment International, In Press, Corrected Proof Available online 23 November 2004, www.sciencedirect.com

L.A. Cox, and P.F. Ricci, Causation in risk assessment and management: models, inference, biases, and a microbial risk–benefit case study, Environmental International, Available online 27 October 2004.

Hurd, H.S. et al. 2004. The Public Health Consequences of Macrolide Use in Food Animals: A Deterministic Risk Assessment. J. Food Protection. 67: 980-992.

Kelly, L. et al. 2004. Animal growth promoters: to ban or not to ban? A risk assessment approach. Int J Antimicrob Agents. 2004 Sep;24(3):205-12.

MMWR. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5316a2.htm

Smith, D. L. et al. 2004. Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: resistance is a regional problem. Proc Natl Acad Sci U S A. 2004 Mar 9;101(10):3709-14. Erratum in: Proc Natl Acad Sci U S A. 2004 Apr 13;101(15):5696.